lines 7-10 and from page 26, line 23 to page 27, line 3.

Claim 5 has been added to specifically recite a recombinant expression vector comprising the nucleotide sequence of SEQ ID NO:1. Support for this claim can be found throughout the specification as originally filed, with specific support being found at least at page 2, lines 5-8, and at page 14, lines 20-27.

Claim 6 has been added to specifically recite a recombinant host cell comprising the expression vector of claim 3. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page 14, lines 27-33.

It will be understood that no new matter is included within the amended or newly added claims.

III. Rejection of Claims 1-4 Under 35 U.S.C. § 101

The Action first rejects claims 1-4 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The Action states that "(t)he specification states that (*sic*) novel human protein (NHP) claimed in the instant application share sequence similarity with mammalian Wnt proteins" (Action at page 2), and since "individual members have distinct, and sometimes even opposite, biological activities" (Action at page 3), the presently claimed sequence lacks a patentable utility. The Action then goes on to cite articles by Bejsovec (Curr. Biol. *9*:R684-R687, 1999) and Martinez Arias *et al.* (Curr. Opin. Genet. Dev. *9*:447-454, 1999) to support the position that different Wnt-family member proteins have different functions. However, this argument is completely irrelevant to the utility of the sequence claimed in the present application. While Applicants do in fact state that the claimed sequence "shares structural similarity with animal Wnt-family proteins" (specification at page 2, lines 3-4), the specification as originally filed also goes on to further characterize the claimed sequence, not just as a random member of the Wnt-family of molecules, but specifically Wnt-14 (specification at page 20, lines 16-17). Furthermore, Applicants would like to invite the Examiner's attention to the fact that a sequence sharing over 99% percent identity at the protein level with the claimed sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists who are *wholly unaffiliated with Applicants* as "Homo sapiens mRNA for WNT14" (Saitoh *et al.*, Biochem. Biophys. Res. Commun. *284*:1168-1175, 2001; GenBank accession number AB060283; alignment, GenBank report, and abstract shown in **Exhibit C**). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described

for the invention to be credible or believable. Given this GenBank annotation, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is human Wnt-14, exactly as set forth by Applicants in the specification as originally filed.

Additionally, the specification as originally filed states that the presently claimed sequence has a role in "cancer" (specification at page 1, line 26), a role that has been confirmed by Kirikoshi *et al.* (Int. J. Oncol. 19:1221-1225, 2001; abstract provided in **Exhibit D**), as well as a role in "development" (specification at page 1, line 26), a role that has been confirmed by Hartmann and Tabin (Cell *104*:341-351, 2001; abstract provided in **Exhibit E**). Given the well established biological and medical relevance of Wnt-14, those of skill in the art would readily appreciate the utility of the present sequence in numerous applications, as described herein below and in the specification as originally filed. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Action cites an article by Skolnick *et al.* ("Skolnick"; 2000, Trends in Biotech. *18*:34-39) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (Skolnick at page 36, emphasis added). However, Skolnick concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional "motifs" present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that "sequence-based approaches to protein-function prediction have proved to be very useful" (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus arguing against the conclusion drawn in the Action. Thus, Skolnick does not suggest a high level of uncertainty in assigning function based on sequence, and thus also does not support the alleged lack of utility.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), in addition to the utility described above, the present invention has a number of other substantial and credible utilities, not the least of which is in "forensic biology", as described in the specification, at least at page 3, line 13. As described in the specification at page 17, lines 12-24, the present sequence defines a number of coding single nucleotide

polymorphisms. Specifically: a silent C/T polymorphism at nucleotide position 153 of SEQ ID NO:1; a C/G polymorphism at nucleotide position 946 of SEQ ID NO:1, which can lead to a glutamine or glutamate residue at amino acid position 316 of SEQ ID NO:2; and a C/A polymorphism at nucleotide position 953 of SEQ ID NO:1, which can lead to an threonine or asparagine residue at amino acid position 318 of SEQ ID NO:2. As such polymorphisms are the basis for forensic analysis, which does not require any information about the function of the encoded protein and is undoubtedly a "real world" utility, the present sequences must in themselves be useful. It is important to note that the presence of more useful polymorphic markers for forensic analysis would not mean that the present sequences lack utility. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Just because other polymorphic sequences from the human genome have been described does not mean that the use of the presently described polymorphic marker for forensic analysis is not a specific utility.

As yet a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 3, lines 3-10, the present nucleotide sequences have a specific utility in "identification of protein coding sequences and mapping a unique gene to a particular chromosome", specifically chromosome 1, as described in the specification at least on page 3, lines 6-7. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 4 coding exons on chromosome 1 (present within the chromosome 1 clone disclosed in Genbank Accession Number AL360269; alignments and the first page from the Genbank report are presented in **Exhibit F**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 1 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). As described in the specification as originally filed at page 3, lines 8-10, the claimed sequences "identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone". The specification also details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification at page 11, lines 16-21). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (2001, Science *291*:1304 at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner questions this utility, stating that this is "a general utility that would be applicable to the broad class of the invention" (Action at page 4). First, this statement is based on a false premise, namely that any DNA has utility in identification of protein coding sequences and intron/exon junctions. It is well known in the art that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequences provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Second, even though other sequences may be useful in identification of protein coding sequences and intron/exon junctions, this does **not** mean that the present sequences lack

a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*). The Examiner seems to be confusing the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, with that of a **unique** utility, which is clearly an improper standard. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, just to name a few particular examples, because examples of each of these have already been described and patented. However, only the briefest perusal of any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, as detailed in the specification, at least on page 6, lines 3-6, the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The present nucleotide sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American Home Products and Rosetta acquired by Merck) were viewed to have such "real world" value that they were acquired

by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established.

The Examiner questions this utility, stating that "without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean" (Action bridging pages 4 and 5). However, this argument is misplaced, since the Examiner seems to be requiring knowledge of the results of the expression profiling study before carrying out the study itself. Expression profiling does not require a knowledge of disease states in which expression of the selected nucleic acid is increased or decreased - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. Regarding whether "significant further research" (Action at page 5) would be required to practice the claimed invention, Applicants point out that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as it is presented in the Sequence Listing, without **any** further experimentation. Although information regarding a particular disease state associated with a particular nucleic acid sequence might make it even more useful in such applications, this does not mean that the presently described nucleic acid sequences lack a specific utility in gene chip applications. Once again, "[A]n invention need not be the best or only way to accomplish a certain result" (*Carl Zeiss Stiftung v. Renishaw PLC, supra*).

Furthermore, the association of a particular disease with the claimed sequence is not the standard required for utility under 35 U.S.C. § 101. In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. Even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The Action further states that the claims lack utility because the specification "does not disclose any working examples demonstrating that specific agonists/antagonists of NHP were used to treat any condition" (the Action at page 5). However, this position as applied to the presently claimed sequences is wholly unsupported by mandatory legal precedent. First, as described above, treatment of disease is not the proper standard for utility under 35 U.S.C. § 101. Second, it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (CCPA, 1962).

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739

(Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section IV, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid

molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-4 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

IV. Rejection of Claims 1-4 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-4 have been shown to have "a specific, substantial, and credible utility", as detailed in section III above, the present rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Rejection of Claims 5 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claims 2 and 4 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Action rejects claim 2 as allegedly indefinite based on the term "highly stringent hybridization conditions", because the specific hybridization and washing conditions are not recited in the claim. Applicants stress that "a claim need not 'describe' the invention, such description being the role of the disclosure". *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). However, while Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance the claim has been revised to recite specific highly stringent hybridization conditions. As the specification provides specific teaching regarding such highly stringent hybridization conditions, at least at page 4, lines 27-30, Applicants submit that revised claim 2 even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request withdrawal of this rejection.

The Action rejects claim 4 as allegedly indefinite based on the term "substantially isolated

protein". While Applicants submit that the term is sufficiently definite, as it is well understood by those of skill in the art that a protein is "substantially isolated" when it is purified from a cell that produces the protein, solely in order to progress the case more rapidly toward allowance the claim has been revised to recite a "purified" protein. As the specification provides specific teaching regarding purification of the proteins of the present invention, at least at page 22, lines 7-10, and from page 26, line 23 to page 27, line 3, Applicants submit that revised claim 4 even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request withdrawal of this rejection.

VI. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner DeBerry have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

May 16, 2003
Date

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Exhibit A

Clean Version of The Pending Claims in U.S. Patent Application Ser. No. 09/997,191

1. (Amended) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes to the nucleotide sequence of SEQ ID NO:1 or the complement thereof under highly stringent conditions of 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1%SDS at 68°C.

3. An isolated recombinant expression vector comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4. (Amended) A purified protein comprising the amino acid sequence shown in SEQ ID NO:2.

5. (New) The recombinant expression vector of claim 3, comprising the nucleotide sequence of SEQ ID NO:1.

6. (New) A host cell comprising the recombinant expression vector of claim 3.

Exhibit B

Marked Up Version of Amended Claims in U.S. Patent Application Ser. No. 09/997,191

1. (Amended) An isolated [cDNA] nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

2. (Amended) An isolated [cDNA] nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes [under highly stringent conditions] to the nucleotide sequence of SEQ ID NO:1 or the complement thereof under highly stringent conditions of 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1%SDS at 68°C.

3. An isolated recombinant expression vector comprising a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO:2.

4. (Amended) [An substantially isolated] A purified protein comprising the amino acid sequence shown in SEQ ID NO:2.

5. (New) The recombinant expression vector of claim 3, comprising the nucleotide sequence of SEQ ID NO:1.

6. (New) A host cell comprising the recombinant expression vector of claim 3.

>AB060283 ACCESSION:AB060283 NID: gi 14530676 dbj AB060283.1 Homo sapiens mRNA for WNT14, complete cds
Length = 1631

Score = 769 bits (1964), Expect = 0.0
Identities = 362/365 (99%), Positives = 363/365 (99%)
Frame = +3

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☐ 1: AB060283. Homo sapiens mRNA...[gi:14530676] Links

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ACCESSION   AB060283
VERSION     AB060283.1  GI:14530676
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  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (sites)
  AUTHORS   Saitoh,T., Hirai,M. and Katoh,M.
  TITLE     Molecular cloning and characterization of WNT3A and WNT14 clustered
            in human chromosome 1q42 region
  JOURNAL   Biochem. Biophys. Res. Commun. 284 (5), 1168-1175 (2001)
  MEDLINE   21308441
   PUBMED   11414706
REFERENCE   2  (bases 1 to 1631)
  AUTHORS   Katoh,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (18-APR-2001) Masaru Katoh, National Cancer Center
            Research Institute, Genetics and Cell Biology Section, Genetics
            Division; Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan
            (E-mail:mkatoh@ncc.go.jp, Tel:81-3-3542-2511, Fax:81-3-3541-2685)
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1: Biochem Biophys Res Commun 2001 Jun 29;284(5):1168-75

Molecular cloning and characterization of WNT3A and WNT14 clustered in human chromosome 1q42 region.

Saitoh T, Hirai M, Katoh M.

Genetics and Cell Biology Section, Genetics Division, National Cancer Center Research Institute, Tsukiji 5-chome, Tokyo, Chuo-ku, 104-0045, Japan.

Human WNT3A and WNT14 cDNAs were cloned and characterized. WNT3A and WNT14 encoded WNT family protein of 352 and 365 amino acids, respectively. The 3.0-kb WNT3A mRNA was moderately expressed in placenta, and the 4.4-kb WNT14 mRNA was moderately expressed in skeletal muscle and heart. Although WNT3A mRNA was not detected in 35 human cancer cell lines, WNT14 mRNA was expressed in gastric cancer cell lines TMK1, MKN7, MKN45 and KATO-III. WNT3A and WNT14 genes, clustered in the head to head manner with an interval of about 58.0 kb, were mapped to human chromosome 1q42 region by fluorescence in situ hybridization. WNT3 and WNT15, clustered in human chromosome 17q21 region, are related genes of WNT3A and WNT14, respectively. WNT3A-WNT14 gene cluster and WNT3-WNT15 gene cluster might be generated due to duplication of ancestral gene cluster, just like WNT10A-WNT6 gene cluster and WNT10B-WNT1 gene cluster. Integration sites of mouse mammary tumor virus (MMTV) are located in the mouse chromosomal regions corresponding to these human WNT gene clusters. These results strongly suggest that unidentified nucleotide motif responsible for susceptibility to recombination might exist within the intergenic regions of these WNT gene clusters. Copyright 2001 Academic Press.

MeSH Terms:

- Amino Acid Sequence
- Chromosome Mapping
- Chromosomes, Human, Pair 1*
- Cloning, Molecular
- DNA, Complementary/analysis
- HL-60 Cells

- Hela Cells
- Human
- K562 Cells
- Karyotyping
- Molecular Sequence Data
- Multigene Family*
- Proteins/genetics*
- Sequence Homology, Amino Acid
- Support, Non-U.S. Gov't

Substances:

- Wnt-3 protein
- WNT14 protein
- Proteins
- DNA, Complementary

Secondary source id:

- GENBANK/AB060284
- GENBANK/AB060283

PMID: 11414706 [PubMed - indexed for MEDLINE]

1: Int J Oncol 2001 Dec;19(6):1221-5 Related Articles, Link

Expression of WNT14 and WNT14B mRNAs in human cancer, up-regulation of WNT14 by IFNgamma and up-regulation of WNT14B by beta-estradiol.

Kirikoshi H, Sekihara H, Katoh M.

Genetics and Cell Biology Section, Genetics Division, National Cancer Center Research Institute, Tokyo 104-0045, Japan.

WNT proteins play key roles in carcinogenesis. We have previously cloned and characterized WNT14 and WNT14B/WNT15. WNT14 and WNT3A genes are clustered on human chromosome 1q42, while WNT14B and WNT3 genes are clustered on human chromosome 17q21. Here, we investigated expression of WNT14 and WNT14B mRNAs in human cancer. WNT14 was significantly up-regulated in 1 out of 9 cases of primary breast cancer. WNT14B was not expressed in primary breast, gastric and colorectal cancers. Among 3 human breast cancer cell lines, WNT14 mRNA was expressed in T-47D cells, and weakly expressed in MCF-7 cells. WNT14 mRNA was also detected in 7 out of 7 pancreatic cancer cell lines, 12 out of 12 esophageal cancer cell lines, 4 out of 4 cervical cancer cell lines, and 5 ou of 7 brain tumor cell lines by using cDNA-PCR. These results indicate that WNT14 rather than WNT14B is preferentially expressed in various types of human cancer, such as breast cancer, gastric cancer, and pancreatic cancer. WNT14 mRNA was up-regulated by interferon gamma (IFNgamma), but no by tumor necrosis factor alpha (TNFalpha), in MKN45 cells derived from gastric cancer, while expression of WNT14B mRNA was not affected by IFNgamma and TNFalpha in MKN45 cells. Although expression of WNT14 mRNA was not affected by beta-estradiol in MCF-7 cells, WNT14B mRNA was transiently up-regulated by beta-estradiol in MCF-7 cells. These results indicate that WNT14 is a target gene of IFNgamma in MKN45 cells, and tha WNT14B is a target gene of estrogen in MCF-7 cells.

PMID: 11713592 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

May 2 2003 16:34:2

1: Cell 2001 Feb 9;104(3):341-51 Related Articles, Link

FULL @ CELL TEXT PRESS

Wnt-14 plays a pivotal role in inducing synovial joint formation in the developing appendicular skeleton.

Hartmann C, Tabin CJ.

Department of Genetics, Harvard Medical School, 02115, Boston, MA, USA

The long bones of the vertebrate appendicular skeleton arise from initially continuous condensations of mesenchymal cells that subsequently segment and cavitate to form discrete elements separated by synovial joints. Little is known, however, about the molecular mechanisms of joint formation. We present evidence that Wnt-14 plays a central role in initiating synovial joint formation in the chick limb. Wnt-14 is expressed in joint-forming regions prior to the segmentation of the cartilage elements, and local misexpression of Wnt-14 induces morphological and molecular changes characteristic of th first steps of joint formation. Induction of an ectopic joint-like region by Wnt-14 suppresses the formation of the immediately adjacent endogenous joint, potentially providing insight into the spacing of joints.

MeSH Terms:

- Animal
- Bone Development*
- Cartilage/embryology
- Cell Differentiation
- Cells, Cultured
- Chick Embryo
- Chondrocytes/metabolism
- Down-Regulation
- Immunohistochemistry
- In Situ Hybridization
- Joint Capsule/physiology*
- Joint Capsule/embryology*
- Models, Biological
- Molecular Sequence Data
- Proteins/physiology*
- Signal Transduction
- Support, Non-U.S. Gov't

- Support, U.S. Gov't, P.H.S.
- Time Factors

Substances:
- WNT14 protein
- Proteins

Secondary source id:
- GENBANK/M74435
- GENBANK/AF153205

PMID: 11239392 [PubMed - indexed for MEDLINE]

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(1098 letters)

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  AUTHORS   Dunn,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (23-MAY-2002) Wellcome Trust Sanger Institute, Hinxton,
            Cambridgeshire, CB10 1SA, UK. E-mail enquiries:
            humquery@sanger.ac.uk Clone requests: clonerequest@sanger.ac.uk
COMMENT     On May 25, 2002 this sequence version replaced gi:20068416.
            During sequence assembly data is compared from overlapping clones.
            Where differences are found these are annotated as variations
            together with a note of the overlapping clone name. Note that the
            variation annotation may not be found in the sequence submission
            corresponding to the overlapping clone, as we submit sequences with
            only a small overlap as described above.
            This sequence was finished as follows unless otherwise noted: all
            regions were either double-stranded or sequenced with an alternate
            chemistry or covered by high quality data (i.e., phred quality >=
            30); an attempt was made to resolve all sequencing problems, such
            as compressions and repeats; all regions were covered by at least
            one plasmid subclone or more than one M13 subclone; and the
            assembly was confirmed by restriction digest. The following
            abbreviations are used to associate primary accession numbers given
            in the feature table with their source databases: Em:, EMBL; Sw:,
            SWISSPROT; Tr:, TREMBL; Wp:, WORMPEP; Information on the WORMPEP
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            http://www.sanger.ac.uk/Projects/C_elegans/wormpep This sequence
            was generated from part of bacterial clone contigs of human
            chromosome 1, constructed by the Sanger Centre Chromosome 1 Mapping
            Group.  Further information can be found at
            http://www.sanger.ac.uk/HGP/Chr1
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